Marked up version of claims

1. (Amended) A method for [treating a subject with a neurological disorder, or at risk of developing a neurological disorder] modifying the function of a target receptor associated with a neurological disorder in a subject comprising:

administering a vaccine comprising a therapeutically effective amount of an antigen, wherein the antigen elicits the production of antibodies in the circulatory system of the subject, or a composition comprising a therapeutically effective amount of an isolated antibody, or an antibody portion, wherein the antibodies bind to a target receptor on a neuronal cell in the central nervous system of the subject, and modify the function of [a target protein in the central nervous system, to treat a neurological disorder in the subject] the target receptor, such that modifying the function of the target receptor protects against a neurological disorder.

3. (Amended) The method of claim 1, wherein the neurological disorder is selected from the group consisting of epilepsy, stroke, Alzheimer's disease, Parkinson's disease, dementia, Huntington's disease, amyloid lateral sclerosis and depression.

9. (Amended) The method of claim 1, wherein the vaccine is selected from the group consisting of a viral vector vaccine, a DNA vaccine, a peptide vaccine and a crude antigen vaccine[, or a combination thereof].

22. (Amended) A method for modifying the function of a target [protein] receptor associated with a neurological disorder in the central nervous system of a subject comprising:

administering a vaccine comprising a therapeutically effective amount of an antigen, wherein the antigen elicits the production of antibodies in the circulatory system of the subject, or a composition comprising a therapeutically effective amount of an isolated antibody, or an antibody portion, wherein the antibodies bind to the target receptor on a neuronal cell in the central nervous system, and directly [modify] modifies the function of [a target protein] the target receptor, or indirectly modifies the function of a process involving the target receptor,

such that the direct, or indirect modification protects against a neurological disorder [in the central nervous system, to thereby modify the function of the target protein].

29. (Amended) The method of claim 22, wherein the vaccine is selected from the group consisting of a viral vector vaccine, a DNA vaccine, a peptide vaccine and a crude antigen vaccine[, or a combination thereof].

36. (Amended) A method for [improving cognition in] modifying the function of a target receptor associated with cognition in the central nervous system of a subject comprising:

administering a vaccine comprising a therapeutically effective amount of an antigen, wherein the antigen elicits the production of antibodies in the circulatory system of the subject, or a composition comprising a therapeutically effective amount of an isolated antibody, or an antibody portion, wherein the antibodies bind to the target receptor, and [modify] modifies the function of [a target protein] the target receptor such that the modification of the target receptor improves cognition in the subject [in the central nervous system, to thereby improve cognition of a subject].

41. (Amended) The method of claim 36, wherein the vaccine is selected from the group consisting of a viral vector vaccine, a DNA vaccine, a peptide vaccine and a crude antigen vaccine[, or a combination thereof].

54. (Amended) A method for [treating a subject with a neuroendocrine disorder, or at the risk of developing a neuroendocrine disorder] modifying the function of a target receptor associated with a neuroendocrine disorder in the central nervous system of a subject comprising:

administering a vaccine comprising a therapeutically effective amount of an antigen [to a subject], wherein the antigen elicits the production of antibodies in the circulatory system of the subject, or a composition comprising a therapeutically effective amount of an isolated antibody, or an antibody portion, wherein the antibodies bind to the target receptor on a

neuronal cell in the central nervous system of the subject, and directly modifies the function of [a target protein in the central nervous system, to thereby treat the neuroendocrine disorder in the subject] the target receptor, or indirectly modifies the function of a process involving the target receptor, such that the direct, or indirect modification protects against a neuroendocrine disorder.

59. (Amended) The method of claim 54, wherein the vaccine is selected from the group consisting of a viral vector vaccine, a DNA vaccine, a peptide vaccine and a crude antigen vaccine[, or a combination thereof].

70. (Amended) A composition comprising a therapeutically effective amount of an NMDA antigen capable of eliciting the production of NMDA antibodies in the circulatory system of the subject, or a therapeutically effective amount of an isolated NMDA antibody, or an antibody portion, wherein the NMDA antibodies bind to an NMDA receptor on a neuronal cell in the central nervous system of a subject, and modify the function of [a target protein] the NMDA receptor in the central nervous system, such that modification of the NMDA receptor protects against a neurological disorder.

74. (Amended) The composition of claim [73] 70, wherein the NMDA antigen is N-methyl-D-aspartate receptor subunit 1 (NMDAR1).

REMARKS

Applicant hereby affirms the election of the invention to group (I), claims 1-3, 5-12, 22, 25-32, 36, 38-44, 54, 56-68, 70 and 72-74. Claims 4, 13-21, 33-35, 47-53, 55-58, 62-67, 69, and 77-85, drawn to non-elected inventions, have been cancelled with traverse. Applicant reserves the right to file a divisional application for non-elected claims. An amendment and response to the final Office Action is submitted in which the Examiner's rejections have been considered. Claims 1-12, 22, 25-32, 36, 38-44, 54, 56-68, 70 and 72-74 are pending in the application. Claims 45, 46 and 73 have been cancelled. Claims 1, 3, 9, 22, 29, 36, 41, 54, 59, 70 and 74 have been amended. New claims 86-108 have been added.

Support for the amendments to the claims can be found throughout the specification, or the claims as originally filed. For example, support for the phrase "a receptor" can be found at page 16, line 13 through page 17, line 30, at page 61, lines 1-11, and at pages 66 through page 73 in Example 6. In particular at page 67, line 4 through page 68, line 14. Support for the term "a neuronal cell" can be found at page 20, line 22, at page 20, line 24, at page 22, line 14, at page 40, line 30. Support for the term "directly modify" can be found at page 14, line 4 through page 15, line 9, in particular, at page 14, lines 28-29, and at page 68, line 13. Support for the term "indirectly modify" can be found at pages 14 , line 22 through page 15, line 9, in particular, at page 14, line 30 through page 15, line 2. Support for the phrase "process involving the receptor" can be found at page 15, lines 2-4, and at page 70, lines 7-11. Support for the new claims can be found throughout the specification and in the claims as originally filed, for example, at pages 45-76. No new matter has been added.

Amendment of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to more particularly point out and distinctly claim the invention to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Applicants respectfully acknowledge that the Examiner has withdrawn some of the substantive rejections of the pending claims.

Rejection of Claims 1-3, 5-12, 22-32, 36-46, 54, 59-61, and 68 Under 35 U.S.C. § 112, First Paragraph

Claims 1-3, 5-12, 22-32, 36-46, 54, 59-61, and 68 remain rejected under 35 U.S.C. §112, first paragraph. In particular, the Examiner asserts that:

> [A]pplicant has not provided evidence to demonstrate treatment of a subject with epilepsy or with a neuroendocrine disorder by administration of a peptide vaccine comprising an NMDAR1 antigen or an antibody. . . Additionally, the working examples with the genetic vaccine in the specification do not provide guidance treatment of subject with a protein vaccine. . . Although the knowledge of peptide vaccines may be known in the art for the treatment of a few diseases, the skilled artisan would not be able to make and use the claimed invention without undue experimentation for the *treatment of epilepsy or other neuroendocrine disorder*. . . (emphasis added).

Although Applicant disagree with the basis of the rejection, in order to expedite prosecution of the application, applicant has amended the claims. The amended claims are no longer drawn to a method of treating neurological disorders, but rather to *modifying the function of a target receptor on a neuronal cell in the central nervous system*, such that modification of the target receptor *protects against a neurological disorder*, *improves cognition* in subject or, *protects against a neuroendocrine disorder*.

Thus, the salient features of the invention involves modifying the function of a target receptor, on a neuronal cell, in the central nervous system of a subject, by using antibodies that are either produced by, or injected into the systemic circulatory system of the subject. The antibodies are raised against a central nervous system antigen, and circulate in the system circulatory system until such time that the blood brain barrier is compromised. When the blood-brain barrier is compromised, the antibodies migrate across the blood-brain barrier into the central nervous system and bind to a target receptor present on a neuronal cell. Upon

binding, the antibody *modifies the function of the target receptor* such that the *modification results in protection against a neurological disorder*, such as epilepsy or stroke. The protection against the neurological disorder can either be from direct modification of the target receptor on the neuronal cell, for example, by inhibiting receptor activity. Alternatively, the protection can arise from an indirect effect of binding to the target receptor, for example, by altering a downstream process or proteins associated with the target receptor.

The specification describes in detail how to generate antibodies against a central nervous system antigen in the systemic circulatory system of a subject, such that the antibodies migrate across the blood-brain barrier when it is compromised, and bind to a target receptor on a neuronal cell. For the sake of example, this has been demonstrated using the NMDA receptor present on a neuronal cell in the central nervous system of a subject. Using NMDAR1 as an antigen for the NMDA receptor, antibodies against the antigen were raised in a rat models of neurological disorders.

In example 3, Applicant has demonstrated the neuroprotective effect against epilepsy using a well established and art recognized animal model for epilepsy. In these experiments, rats were vaccinated with a gene encoding an NMDAR1 antigen. Circulating antibodies were produced in the circulatory system of these animals soon after vaccination. The presence of these antibodies was detected in the blood at 4 weeks post vaccination, and continued to remain in the circulation for at least 4 months afterwards (*See* Figure 3B, lanes 3 and 4, respectively).

Applicant demonstrated the neuroprotective effect of these circulating antibodies by inducing epileptic seizures in these animals. In Example 3, Applicant shows that the circulating antibodies were able to cross the blood-brain barrier that was compromised by the kainate-induced seizures. After crossing the blood-brain barrier, the antibodies were able to bind to the target receptor on the neuronal cell, in the central nervous system of the animal *i.e.*, the NMDA receptor, and modify the function of the target receptor to protect the animal from having seizures. Fig. 4A clearly shows no signs of electrographic seizure activity in animals with antibodies against NMDAR1, demonstrating the neuroprotective effects of the

circulating antibodies. In contrast, control animals vaccinated with AAVlac, were not protected and developed seizures within 10 minutes of kainate drug administration.

The neuroprotective effect was not only measured by outward appearance of the animals, *i.e.*, seizures, but also by isolating the brains of these animals and using immunochemistry techniques. Neuronal death typically occurs as a result of seizures. The results showed that neuronal death in the hippocampus only occurred in animals that were not treated with the neuroprotective vaccine. In contrast, those animals which had previously been vaccinated, and did not have seizures, were protected and did not display signs of hippocampal injury (*See* Example 3, page 59, and at page 3, lines 2-7).

Applicant also demonstrates the anti-stroke and ischemic neuroprotection efficacy of the neuroprotective vaccine using an art recognized animal model for stroke (*See* Example 4, at page 64). Animals with circulating antibodies displayed a much reduced total infarct volume in the ipsilateral stratium and/or cortical regions (approx. $19.2+6.2$ mm^3) compared to those animals that were not treated (approx. $66.4 +12.4mm^3$).

Applicant further demonstrates that the neuroprotective effect of the neuroprotective vaccine can occur either by directly modifying the function of the target receptor, or by modifying the function of a downstream process that involves the target receptor *i.e.*, indirect modification.

Applicant demonstrates the neuroprotection effect of the vaccine resulting from direct modification of the NMDA receptor using fluorescent calcium loading techniques (*See* Example 6, at page 66). To demonstrate this direct modification of the NMDA receptor on a neuronal cell, circulating IgG antibodies produced in rats vaccinated with the neuroprotective vaccine were isolated. These isolated IgG antibodies were incubated *in vitro* with cultured primary neuronal cells which express the NMDA receptor. The cultured neuronal cells treated with the isolated IgG antibodies did not display an increase in fluorescent signal compared with control cells (cultured neuronal cells treated with the IgG antibodies isolated from animals treated with AAVlac as a positive control). These results show that the IgG antibodies isolated

from the NMDAR1 vaccinated animals bind to the NMDA receptor expressed in cultured neuronal cells, and blocks the increase in calcium uptake by these NMDA receptors. This demonstrates the *direct* modification of the NMDA receptors by the IgG antibodies. In contrast, there was an increase in the calcium signal in untreated cultured neuronal cells, or those treated with IgG antibodies isolated from animals treated with AAVlac because there were no NMDA antibodies to block calcium uptake by the NMDA receptors.

As a result of the circulating antibodies binding to a target receptor and modifying its function, downstream processes that involve the target receptor may also modified, *i.e.,* indirect modification. To demonstrate that the circulating antibodies can *indirectly* effect processes associated with the NMDA receptor, Applicant investigated the expression of the Krox-24 protein, a protein typically activated by the NMDA receptor (*See* page 70, line 8 through page 71, line 12). The results show that the levels of Krox-24 protein were significantly reduced within the cortical brain regions of animals treated with the NMDA neuroprotective vaccine (*See* Fig. 10 C). This data shows that the circulating antibodies not only *directly* modify the NMDA receptor by binding to it, but also *indirectly* modify other processes or proteins involved with the NMDA receptor.

Applicant has also demonstrated the improvement in cognition using the neuroprotective vaccine. In Example 7, Applicant describes the effect of the NMDA vaccine on learning and memory by performing a series of behavioral tests on the vaccinated animals. The results from the various behavioral test demonstrated that the vaccinated animals showed a significantly improved performance, for example in the Barnes maze test (page 74, lines 3-6), and had improved contextual memory in the freezing response test (page 74, lines 11-20).

For all the forgoing reasons, the Examiner is respectfully requested to withdraw the rejection.

Rejection of Claims 70-76 Under 35 U.S.C. §112, First Paragraph

Claims 70-76 have been rejected under 35 U.S.C. § 112, first paragraph. In particular, the Office Action asserts

> [t]he specification while being enabling for a composition comprising an effective amount of a mouse NMDAR1 antigen capable of eliciting the production of antibodies in the circulatory system of the subject or an amount of an isolated mouse anti-NMDAR1, does not reasonably provide enablement for a composition comprising a therapeutically effective amount an antigen capable of eliciting the production of antibodies in the circulatory system of the subject or an amount of an isolated antibody or a portion . . .

While disagreeing with the basis of the rejection, in order to expedite prosecution of the application, Applicant has amended claim 70 and dependent claims thereof the recite a composition comprising an *NMDA* antigen capable of eliciting the production of *NMDA antibodies*, rather than any antigen or antibody. Applicant has provided ample guidance on a composition comprising a therapeutically effective amount of an NMDA antigen, or antibodies that bind to, and modify the function of an NMDA receptor to protect against a neurological disorder.

For example, Applicant has described how to make a construct used in the composition that includes an NMDA antigen such as the NMDAR1 antigen. Applicant also provides guidance for other NMDA antigens that can readily be substituted using Applicant's disclosure. For example, at page 16, line 14 through page 17, line 13 Applicant describes other NMDA receptors subunit families and provides a number of reference citations that the skilled artisan could use for further information. Applicant provides methods and protocols for using the NMDA construct in the formulation of a vaccine to inject into *in vivo* animal models of neurological disorders, such as epilepsy and stroke (*See* Examples 3 and 4, respectively). The therapeutic amount of the vaccine required can be determined by the desired result, for example, in the case of epilepsy, the therapeutic amount of an antigen is the amount of antigen

resulting in antibodies that protect against seizures. Applicant also provides a number of behavioral tests to determine the cognition effects of the composition.

Based on the adequate amount of teaching and guidance provided by Applicant's specification, the skilled artisan could readily produce a composition with any other NMDA subunit using the same methodology without undue experimentation. Accordingly, for all the foregoing reasons, Applicant respectfully requests that the Examiner withdraw the rejection.

Rejection of Claims 9, 29, 41, and 59 Under 35 U.S.C. §112 Second Paragraph

Claims 9, 29, 41, and 59 have been rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Office Action asserts that the phrase 'or a combination thereof' renders the claims vague and indefinite."

In response, applicants have removed the offending phrase, as suggested by the Examiner, thereby rendering the rejection moot.

CONCLUSION

In summary, the above-identified patent application has been amended and reconsideration is respectfully requested for all the reasons set forth above. The Examiner is urged to telephone the undersigned Agent for Applicant in the event that such communication is deemed to expedite prosecution of this matter.

Respectfully submitted,

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